REMARKS/ARGUMENTS

In this Reply to the Office Action dated July 25, 2003, Applicant has amended Claims 25, 26, 27, 29 and 30, and added Claims 59-70. Claim 28 has been cancelled. Therefore, upon entry of this amendment, Claims 25-30 and 59-70 will be before the Examiner for consideration. No new matter is presented.

Rejection Under 35 USC § 112, first paragraph

Claims 25-29 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. According to the Office Action:

> SEQ ID NO:2, and 11 and 12 meet the written description requirements of 35 USC 112, first paragraph. However, the claims are directed to encompass agents that inhibit expression of gene sequences, sequences that hybridize to SEQ ID NO:2, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology) and so forth....None of these sequences meet the written description provision of 35 USC 112, first paragraph.

In response, Claim 25 has been amended to recite "(a) providing a cell that expresses a SIM2 short form nucleic acid having the sequence of SEQ ID NO:2 and; (b) introducing into the cell an agent that decreases the expression of a nucleic acid having the sequence of SEQ ID NO:2 or a complement of SEQ ID NO:2 in the cell." Corresponding amendments have been made to Claims 26 and 27.

Also in reference to the rejection under 35 U.S.C. § 112, first paragraph, the Office Action asserts:

> The specification fails to describe what features (i.e. structures) of any particular agent would be expected to impart the predictable function of inhibiting a SIM2 of SEQ ID NO:2...as defined by the specification....One in the art does not know based on the instant specification what agents could be used in the instant invention and further do not know the structure of the scope of the SIM2 genes instantly targeted, for example. It is noted

> that the instantly claimed invention (claims 25-29) is not even limited to a direct inhibition of SIM2 but also reads on inhibitors that may indirectly inhibit the expression of SIM2 short form....Claim 28 requires that the antisense oligonucleotide hybridize to a SIM2, which clearly implies that such hybridization is not required in the method of claim 27, for example....The species specifically disclosed are not representative of the genus because the genus is highly variant.

Applicant has reviewed the Guidelines for the Examination of Patent Applications Under 35 U.S.C. § 112, ¶1, "Written Description" Requirement, published in Fed. Reg. Vol. 66, No. 4, January 5, 2001 and believes the claims recited herein to be patentable under § 112, ¶1 as interpreted in applicable case law cited therein. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc. 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. Hybritech Inc. v. Monoclonal Antibodies, Inc. 802 F.2d at 1384, 231 USPQ at 94.

Applicant respectfully disagrees that those of skill in the art would not know based on the instant specification what agents could be used to inhibit expression of a SIM2 short form nucleic acid. (As for the alleged uncertainty regarding the specific structure of the targeted SIM2 sequences, clarification on that point is provided by the amendments discussed *supra*.) In

contrast to the Examiner's statement, Applicant submits that the specification provides extensive written description of agents that can inhibit expression of SIM2 nucleic acids. In particular, the section entitled "Antisense, Ribozyme, Triplex Techniques," spanning four pages of text (p. 12, line 15- p. 16, line 24), describes several agents capable of inhibiting expression of a specific gene such as SIM2. The structures of agents that would be expected to impart the predictable function of inhibiting a nucleic acid such as SIM2 were well known to those of skill in the art at the time the invention was made. The structure of those agents is dictated primarily by the structure (i.e., nucleic acid sequence) of the target DNA or RNA molecules to which they hybridize. The instant section of the specification provides extensive description of design and use of inhibitory oligonucleotides that hybridize to either DNA (triple helix) or RNA (antisense and ribozymes) encoding a SIM2 short form nucleic acid, and further refers to patents and standard references in the field, for example to Van der Krol et al., 1988 regarding design of antisense oligonucleotides (p. 13, line 1) and, regarding ribozymes, to Lewin and Hauswirth, 2001, and other references (p. 15, lines 6-9). Claim 26 as amended recites exemplary inhibitory oligonucleotides, such as antisense oligonucleotides, ribozymes and triple helix forming molecules. Claim 59, depending from Claim 26 as amended, has been added to recite a ribozyme. Claim 60 has been added to recite a molecule that forms a triple helix with a promoter region of a SIM2 short form nucleic acid.

The Office Action asserts that "[c]laim 28 requires that the antisense oligonucleotide hybridize to a SIM2, which clearly implies that such hybridization is not required in the method of claim 27." Claim 27 as amended herein now recites an antisense oligonucleotide that hybridizes to "a nucleic acid having a sequence that is a complement of a nucleic acid having the

sequence of SEQ ID NO:2." Former Claim 28 has been cancelled. Claim 29 has been amended to depend from Claim 27.

As stated above, those of skill in the art were in possession of the general knowledge of how to design inhibitory oligonucleotide sequences at the time the invention was made. Regarding construction of SIM2 antisense oligonucleotides, the specification (p. 13, lines 12-18) describes antisense oligonucleotides that are complementary to the 5' untranslated end of the mRNA sequence, to the 3'-untranslated region of the message, and to the coding sequence. Claim 61, depending from Claim 29 as amended, has been added reciting this limitation. The specification further provides specific structural guidance, stating, for example, that "[w]ith respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site e.g., between the -10 and +10 regions of a SIM2 protein-encoding nucleic acid sequence are preferred" (p. 13, lines 2-4). Claim 62, dependent from Claim 61, has been added relating to limitation. Claim 63 recites the use of antisense oligonucleotides that hybridize to selected polynucleotide sequences in the vicinity of the 3'-untranslated region of the SIM2 short form sequence (i.e., between the +1753 and +1853 positions of SEQ ID NO:2). Additionally, the structures of specific antisense and control sequences (i.e., SEQ ID NOS:11-13) are disclosed in the specification. The target of SEQ ID NO: 12 is within the region cited in Claim 63. Use of the described sequences is demonstrated in examples, such as Example 20 (p. 37, line 28- p. 38, line 23).

No art was cited relating to Claim 30. Claim 30 was objected to for depending upon a rejected base claim. Claim 30 has been rewritten in independent form including all of the limitations of the base claim and any intervening claims. New claims 64-70 depend from Claim 30 as amended. Claims 64 and 65 relate to the antisense oligonucleotide of Claim 30 with a

modified phosphate backbone. Support for this is found in the specification on p. 14, lines 13-17. Claims 66 and 67 relate to the antisense oligonucleotide of Claim 30 with at least one modified sugar moiety. See specification, p. 14, lines 12-13. Claim 68 relates to an antisense oligonucleotide with at least one modified base. A list of exemplary modified bases is presented on p. 14, lines 1-12 and lines 19-22 of the instant specification. Claim 69, dependent from claim 68, recites an oligonucleotide in which a modified base is a 2'-O-methylribonucleotide, and Claim 70, which also depends from Claim 68, recites a chimeric RNA-DNA analog of SEQ ID NO:12. Specific support for the modifications in Claims 69 and 70 is found in the specification on p. 14, lines 19-22.

Applicant has overcome the 35 U.S.C. § 112, first paragraph rejections based on the amendments presented above. Because the 35 U.S.C. §112, first paragraph rejections were overcome, Applicant submits that Claims 25-30 are allowable. Similarly, it is believed that added Claims 59-70 are allowable.

Rejection Under 35 U.S.C. § 103(a)

Claims 25-29 were rejected under 35 USC §103(a) as being unpatentable over Kong et al. (FASEB Journal, Vol. 15(5):A762, March 3, 2001; "Kong") and Chrast et al. (cited by Applicant) in view of Agarwal et al. (Molecular Medicine Today, Vol. 6:72-81, February 2000; "Agarwal") and Sharma et al. (Bioessays Vol. 17:1055-1063, 1995; "Sharma").

As described in the specification (p. 1, lines 27-33 and p. 2, lines 1-8), Chrast teaches the molecular cloning and sequencing of SIM2 long and short form genes, associated with Down's syndrome. Chrast does not teach the use of antisense oligonucleotides directed against SIM2. Kong et al. teaches the use of antisense oligonucleotides directed against SIM2 to study lung development *in vitro*. However, the teaching of Kong is of no consequence because Kong is not

a prior art reference. The publication date of Kong is March 31, 2001. Applicant's invention claims the priority of two U.S. Provisional patent applications (i.e., Ser. No. 60,223,531, filed August 4, 2000, and Ser. No. 60/257,965, filed December 22, 2000). Antisense oligonucleotide sequences directed against SIM2 nucleic acids are disclosed in both of the provisional applications. Because the primary reference (Chrast) does not disclose antisense oligonucleotides directed against SIM2, and because Kong is not prior art, the combination of these references with the other cited references is moot. Accordingly, Applicant has overcome the rejection under 35 USC § 103(a).

Applicant has made every effort to present claims which distinguish over the cited art, and it is believed that all claims are in condition for allowance. However, Applicant invites the Examiner to call the undersigned if it is believed that a telephonic interview would expedite the prosecution of the application to an allowance.

Respectfully submitted,

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